

Remarks*A. Status of Claims*

Claims 21–33 remain pending. Each of those claims has been amended. No new matter has been added.

B. Restriction

Applicants confirm their previous election without traverse of claims 21–33, which are the Group III claims. As to the species restriction, the Office appears to have made a typographical error in paragraph 4 of page 3 of the office action. Applicants elected, without traverse, the species of claim 30 (not claim 33). *See* Response mailed Jan. 22, 2003.

C. Section 102 Rejections

Claims 21, 27, and 30–33 stand rejected under 35 U.S.C. § 102 as being anticipated independently by U.S. Patent No. 5,145,684 (“Liversidge”), U.S. Patent No. 5,542,935 (“Unger”), and U.S. Patent No. 5,213,788 (“Ranney”). In view of the amendments and comments below, Applicants respectfully traverse.

Claim 21 has been put in the form of a method claim. Applicants believe that the process-like limitations of original claim 21 should have been treated as explicit limitations by the Office in rendering the present office action. However, in the spirit of cooperation, the form of that claim has been modified to recite a method in order to address the Examiner’s concerns. Applicants respectfully submit that the process limitations of amended claim 21 must be considered.

The amendments do not introduce elements that were not already generally present within the elected claims. Accordingly, it is believed that the present amendments do not affect Applicants’ previous election of claims. Further, it is believed that the amendments do not necessitate any new search because, as is apparent from the present office action, the Office has

already rendered its opinion about the process-like limitations of claim 21. In fact, the Office has already relied upon art for support of its opinions. *See, e.g.*, office action, pages 6–7 (discussing oil-in-water process limitations and comparing those limitations with the cited Bosch and Agostiano references).

Amended claim 21 requires the preparation of a particular microemulsion (an oil-in-water microemulsion including a matrix material, a surfactant or co-surfactant, and a molecule of interest) by heating, which is then cooled to form a nanoparticle associated with a molecule of interest (entrapped in or adsorbed to the nanoparticle). It is clear that none of the cited anticipation references—Liversidge, Unger, and Ranney—disclose or even suggest all those features, nor has the Office pointed to any evidence or passages indicating otherwise. Accordingly, amended claim 21 is not anticipated or otherwise rendered unpatentable, and the current rejection should be withdrawn. If the Examiner disagrees, Applicants request citation to specific portions of any one of these references disclosing, for instance, the recited making of a microemulsion by heating including the listed ingredients, the recited cooling step that forms a nanoparticle, and the recited molecule of interest.

D. Section 103 Rejections

Dependent claims 22–26 and 28–29 stand rejected under 35 U.S.C. § 103 as being rendered obvious by U.S. Patent No. 5,510,118 (“Bosch”) along with the journal article Micron, 31:253-258, 2000 (“Agostiano”). Applicants respectfully traverse.

Certain general limitations from claim 22 have been incorporated into claim 21, so this rejection will be discussed primarily in relation to amended claim 21. Amended claim 21 requires, among other things, cooling a particular microemulsion to form a nanoparticle. Neither

Bosch nor Agostiano teach or suggest such a cooling step, nor do they teach the particular microemulsion that acts as the nanoparticle precursor.

Bosch is directed to a process of preparing nanoparticulate drug substances that involves: preparing a premix of the drug substance and subjecting the premix to *mechanical means to reduce the particle size* of the drug substance. Abstract. Nowhere is there a disclosure or even a suggestion of: (a) the particular oil-in-water microemulsion of amended claim 21 or (b) cooling that microemulsion in order to form a nanoparticle. In contrast, Bosch appears to simply teach the mechanical reduction of particle size of dispersions of crystalline drug substances and surface modifiers. *See, e.g.*, col. 4, lines 6–11. Moreover, there is no motivation to modify Bosch so that the microemulsion and cooling steps of amended claim 21 would be implicated, nor is there any evidence that modifying Bosch to become closer to amended claim 21 would have a reasonable expectation of success. If the Examiner disagrees, specific citations to portions of Bosch that rebut Applicants' assertions are requested.

Agostiano is directed to a microemulsion that is processed by evaporation at an elevated temperature to form solids. *See, e.g.*, page 255, section 2.4. As is the case with Bosch, nowhere in Agostiano is there a disclosure or even a suggestion of: (a) the particular oil-in-water microemulsion of amended claim 21 or (b) cooling that microemulsion in order to form a nanoparticle. In contrast, Agostiano appears to synthesize a microemulsion and then evaporate it to dryness at 60°C to form a solid, which is then dissolved, centrifuged, washed, dried under a N₂ stream, and stored in the dark as a powder. *See* page 255, section 2.4. Moreover, there is no motivation to modify such teaching so that the particular oil-in-water microemulsion and cooling steps of amended claim 21 would be implicated, nor is there any evidence that modifying Agostiano to become closer to amended claim 21 would have a reasonable expectation of

success. If the Examiner disagrees, specific citations to portions of Agostiano that rebut Applicants' assertions are requested.

Because neither Bosch nor Agostiano disclose, teach, or suggest cooling the recited microemulsion of amended claim 21 to form a nanoparticle, there can be no *prima facie* case of obviousness even if Bosch and Agostiano are combined—even in combination, the references lack explicit elements of claim 21. Moreover, there is no motivation to modify the subject matter of the references to achieve the present invention, nor is there any evidence to suggest that such a modification(s) would have a reasonable chance of success. In sum, there is no evidence of obviousness, and amended claim 21 is allowable. For at least the same reasons, claims 22–26 and 28–29, which depend from claim 21, are allowable as well. For instance, claim 22 requires (among other things) particular temperature ranges for heating and cooling steps, which are absent from the cited art. Applicants respectfully request removal of the current rejection so that the claims can pass to issuance.

E. Examiner Interview

On August 6, 2003 Applicants' representative conducted a personal interview with the Examiner and his supervisor for this file. During that interview, the parties discussed the rejections and arguments outlined in this response. The Examiner presented new art for Applicants' consideration and comment—U.S. Patent No. 5,496,811 (“Aviv”). Finally, the Office advised that, in its opinion, the term “emulsifying wax” (see claim 23) did not comply with 35 U.S.C. § 112, 2nd paragraph.

1. Aviv Does Not Render the Present Application Unpatentable

Amended claim 21 is directed to a method of making a nanoparticle and requires, among other things, the making of a particular microemulsion by heating, and cooling the

microemulsion to form the nanoparticle. The present patent application provides a definition of “microemulsion” within the specification. *See* specification, p. 13.

Aviv, in contrast, does not involve microemulsions, much less disclose or suggest the method for making a nanoparticle using a microemulsion, as recited in claim 21. Aviv, instead, is directed to “submicron emulsions,” which are formed by shear forces and homogenization and which are explicitly *distinguished* from emulsions and microemulsions. [*See* Aviv, Title, Abstract, col. 2, lines 18-28 (providing definitions for emulsion, macroemulsion, and microemulsion), col. 4, lines 28-35 (providing a definition for submicron emulsion and distinguishing it from a microemulsion)]. Accordingly, the disclosure of Aviv concerning submicron emulsions cannot amount to a disclosure or suggestion of the recited techniques for making nanoparticles using *microemulsions*. Further, no motivation is provided in the art to modify Aviv so that it would yield a microemulsion or so that it would suggest a method for making a nanoparticle using such a microemulsion. Still further, there is no evidence that any such modification to Aviv would have a reasonable expectation of success. Aviv therefore cannot not render claim 21, or any of its dependent claims, unpatentable. No *prima facie* case can be established based on Aviv.

Moreover, nowhere does Aviv disclose or suggest cooling a substance *to form a nanoparticle* as recited by claim 21. It appears that the cooling step of Aviv does not form nanoparticles. [Aviv, col. 7, line 47 - col. 8, line 7]. Instead, it appears that Aviv uses homogenization and filtering to yield a submicron emulsion, which Aviv explicitly distinguishes from microemulsions.¹ *Id.* Again, Aviv cannot render any pending claim unpatentable.

¹ Clearly, the present claims do not exclude the use of additional steps, such as homogenization and/or filtering to promote particle formation. However, it is Applicants’ position that Aviv does not teach or suggest forming nanoparticles from cooling *per-se*.

2. *The Phrase "Emulsifying Wax" Is Clear*

There is no evidence that the phrase "emulsifying wax" lacks the clarity or precision required by Section 112, 2nd paragraph and its associated case-law. "Emulsifying wax" is a phrase well-known in the art, as evidenced by the exemplary, non-limiting entry provided in Appendix A. Applicants respectfully submit that the use of "emulsifying wax" does not render any claim indefinite, and a rejection based on that phrase would not be warranted.

F. *Conclusion*

Applicants believe that this submission fully responds to all outstanding matters for this application. Applicants respectfully request the withdrawal of all claim rejections and the mailing of a notice of allowance. All the claims are patentably distinct from the cited art.

Should the Examiner have any questions or desire to sustain *any* rejections, the courtesy of a telephone conference is respectfully requested in advance so that all pending matters may be more efficiently and courteously resolved.

1995

USP 23

NF 18

THE UNITED STATES PHARMACOPEIA
THE NATIONAL FORMULARY

*By authority of the United States Pharmacopeial
Convention, Inc., meeting at Washington, D.C.,
March 8-10, 1990. Prepared by the Committee of
Revision and published by the Board of Trustees*

Official from January , 1995



UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

NOTICE AND WARNING

Concerning U.S. Patent or Trademark Rights
The inclusion in the Pharmacopeia or in the National Formulary of a monograph on any drug in respect to which patent or trademark rights may exist shall not be deemed, and is not intended as, a grant of, or authority to exercise, any right or privilege protected by such patent or trademark. All such rights and privileges are vested in the patent or trademark owner, and no other person may exercise the same without express permission, authority, or license secured from such patent or trademark owner.

Concerning Use of USP or NF Text
Attention is called to the fact that USP and NF text is fully copyrighted. Authors and others wishing to use portions of the text should request permission to do so from the Secretary of the USPC Board of Trustees.

© 1994 The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway, Rockville, MD 20852.
All rights reserved

ISBN 0-913292-76-4 (cloth)
0-913292-81-0 (leather)

Printed by Rand McNally, 1133 County Street, Taunton, MA 02780-3795.

Purified Vegetable Oil

Purified Vegetable Oil is a mixture of tri-
of fatty acids. The melting range, heavy
iodine value, and saponification value
depending on Type, as set forth in the accom-
table.

	Type I	Type II
Melting range, Class II (741)	57° to 70°	20° to 50°
Iodine value, Method II (231)	10 ppm	0.001%
Acid value, Method II (401)	0 to 5	55 to 80
Saponification value (401)	175 to 205	185 to 200

Packaging and storage—Preserve in tight containers, in a cool

Label it to state whether it is Type I or Type II.

Labeling (791)—Dry it at 105° for 4 hours: it loses not
0.1% of its weight.

(401)—Weigh accurately 20 g into a conical flask,
steam bath, add 100 mL of hot alcohol that previously
neutralized with 0.1 N sodium hydroxide to phenol-
phthalein TS, swirl, and add 1 mL of phenolphthalein TS. Titrate
with sodium hydroxide until the solution remains faintly
being shaken for 15 seconds: the acid value is not
more than 5.

Saponification value (401): not more than 0.8%.

For Injection—see Water for Injection USP

For Injection, Sterile—see Water for
Injection, Sterile USP

For Irrigation, Sterile—see Water for
Injection, Sterile USP

Peppermint—see Peppermint Water

Purified—see Water, Purified USP

Stronger Rose—see Rose Water, Stronger

Carnauba Wax

Carnauba Wax is obtained from the leaves of *Co-*
cerifera Mart. (Fam. Palmae).

Packaging and storage—Preserve in well-closed containers.

Melting range, Class II (741): between 81° and 86°.

(401)—Weigh accurately 3 g into a 250-mL flask attached
reflux condenser, add 50 mL of a mixture of isopropyl alcohol
benzene (5:4), and boil gently until the wax is completely
dissolved. Remove the flask from the condenser, add about 1
mL of phenolphthalein TS, and titrate with 0.5 N alcoholic po-
tassium hydroxide VS to a faint, reddish yellow color. Calculate
acid value as the number of mg of potassium hydroxide re-
quired to neutralize the free acids in 1 g of Carnauba Wax. The
acid value so obtained is between 2 and 7.

Saponification value (401)—To the solution from the test for
acid value add 15.0 mL of 0.5 N alcoholic potassium hydroxide
solution for 3 hours, and titrate the excess alkali with 0.5 N
acetic acid VS to a yellow-amber color. Perform a blank
determination (see *Residual Titrations under Titrimetry* (541)).
Saponification value is the summation of the ester value so
obtained and the Acid value; and it is between 78 and 95.

Ignition (281)—Heat 2 g in an open porcelain or
platinum dish over a flame: it volatilizes without emitting an

acid odor. Ignite: the weight of the residue does not exceed 5
mg (0.25%).

Heavy metals, Method II (231): 0.004%.

Wax, Cetyl Esters—see Cetyl Esters Wax

Emulsifying Wax

» Emulsifying Wax is a waxy solid prepared from
Cetostearyl Alcohol containing a polyoxyethylene de-
rivative of a fatty acid ester of sorbitan.

Packaging and storage—Preserve in well-closed containers.

Melting range (741): between 50° and 54°, the following method
being used. Melt a quantity of the test substance slowly, while
stirring, until it reaches a temperature of 90° to 92°, remove the
source of the heat, and allow the molten substance to cool to a
temperature of 8° to 10° above the expected melting point. Chill
the bulb of a suitable thermometer (see *Thermometers* (21)) to
5°, wipe it dry, and while it is still cold, dip it into the molten
substance so that the bulb is completely covered. Withdraw it
immediately, and hold it vertically away from the heat until the
surface dulls. Fix the thermometer securely in a test tube so that
the lower point is 15 mm from the bottom of the test tube. Place
the test tube in a water bath at 10° to 15° and allow it to remain
at that temperature for 30 minutes. Raise the temperature of
the bath at the rate of 2° per minute to 30°, then change to a
rate of 1° per minute, and note the temperature at which the
first drop of melted substance leaves the thermometer. Repeat
the determination twice on a freshly melted portion of the test
substance. If the variation of three determinations is less than
1°, take the average of the three as the melting point. Otherwise,
make two additional determinations, and take the average of the
five.

Hydroxyl value (401): between 178 and 192.

Iodine value (401): not more than 3.5.

Saponification value (401): not more than 14.

pH (791): between 5.5 and 7.0, in a dispersion (3 in 100).

Microcrystalline Wax

» Microcrystalline Wax is a mixture of straight-
chain, branched-chain, and cyclic hydrocarbons, ob-
tained by solvent fractionation of the still bottom
fraction of petroleum by suitable dewaxing or deoiling
means.

Packaging and storage—Preserve in tight containers.

Labeling—Label it to indicate the name and proportion of any
added stabilizer.

Color—Melt about 10 g on a steam bath, and pour 5 mL of the
liquid into a clear-glass, 16- × 150-mm bacteriological test tube:
the warm, melted liquid is not darker than a solution made by
mixing 3.8 mL of ferric chloride CS and 1.2 mL of cobaltous
chloride CS in a similar tube, the comparison of the two being
made in reflected light against a white background, the tubes
being held directly against the background at such an angle that
there is no fluorescence.

Melting range, Class III (741): between 54° and 102°.

Consistency—

Apparatus—Determine the consistency of Microcrystalline Wax
by means of a penetrometer fitted with a polished metal needle